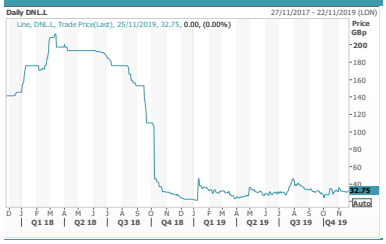
Pharmaceuticals & Biotechnology



Source: Refinitiv

Market data	
EPIC/TKR	DNL
Price (p)	33.0
12m High (p)	46.5
12m Low (p)	21.0
Shares (m)	84.5
Mkt Cap (£m)	27.9
EV (£m)	18.7
Free Float*	40%
Market	AIM

**As defined by AIM Rule 26*

Description

Diurnal is a UK-based specialty pharma company targeting patient needs in chronic, potentially life-threatening, endocrine (hormonal) diseases. Alkindi received approval in 2018 in Europe and is generating revenues; Chronocort has completed the largest and only Phase III trial globally in CAH.

Company information

CEO	Martin Whitaker
CFO	Richard Bungay
Chairman	Peter Allen
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	www.diurnal.co.uk

Key shareholders

Directors	3.0%
IP Group	40.7%
Finance Wales	13.6%
Polar Capital	7.8%
Richard Griffiths	5.9%
Oceanwood Capital	3.7%

Diary

4Q'19	Alkindi US NDA submission
4Q'19	Chronocort EMA MAA

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DIURNAL GROUP

Successful DITEST Phase I trial outcome

Diurnal (DNL) is a commercial-stage specialty pharmaceutical company focused on diseases of the endocrine system. Its two lead products, Alkindi and Chronocort, are in late-stage clinical trials, with Alkindi already licensed in Europe. With the successful outcome of the Phase I trial with DITEST, an oral testosterone replacement formulation, DNL is building on its vision of becoming a leading speciality endocrinology company. The study showed that DITEST was safe, well tolerated and well absorbed in men affected by hypogonadism. DNL will engage with the regulators for the next trial stage, which is likely to be run with a partner.

- **Strategy:** DNL's goal is to create a valuable 'Adrenal Franchise' that can treat patients with chronic cortisol deficiency diseases from birth and for the rest of their lives. The long-term aim, once Alkindi and Chronocort are established in Europe and the US, is to grow the product offering to other endocrine conditions.
- **Trial outcome:** DNL met both primary and secondary endpoints in the Phase I proof-of-concept trial with its testosterone replacement product, DITEST. The product has been shown to be safe, well tolerated, and potentially superior to current oral treatments; this was demonstrated in both fed and fasted states.
- **Market need:** Despite a number of testosterone products available in the market, there is still a strong unmet medical need for an oral medication that would allow safe and better compliance for the patient. DITEST will be an added-value product in the $4.8bn testosterone replacement market.
- **Risks:** Concerns about the US prospects for Chronocort have been allayed by the positive EMA Scientific Advice and the opportunity to revise its US Phase III protocol. However, this has added extra time to the US development process, delaying the point at which DNL should become cashflow-positive.
- **Investment summary:** Alkindi, a cortisol replacement therapy designed for children under 18 years of age, is DNL's first product on the market. It is expected to be followed by Chronocort for adults – a larger market – which now has a clear pathway for regulatory approval in both Europe and the US. Despite this, the share price is still languishing well below valuations determined by peer group and DCF (202p) analyses, due possibly to the need for more capital during 2020.

Financial summary and valuation

Year-end Jun (£m)	2017	2018	2019	2020E	2021E	2022E
Sales	0.00	0.07	1.04	2.14	5.56	15.99
SG&A	-3.23	-6.21	-5.83	-7.52	-9.22	-10.92
R&D	-8.34	-10.02	-8.69	-9.43	-8.96	-11.20
EBITDA	-12.07	-16.97	-14.50	-16.00	-14.25	-8.73
Underlying EBIT	-12.08	-16.98	-14.53	-16.02	-14.27	-8.76
Reported EBIT	-12.08	-16.98	-14.53	-16.02	-14.27	-8.76
Underlying PBT	-12.16	-17.11	-14.40	-15.98	-14.27	-8.83
Statutory PBT	-12.16	-16.91	-14.40	-15.98	-14.27	-8.83
Underlying EPS (p)	-18.04	-27.16	-14.54	-12.88	-11.27	-5.69
Statutory EPS (p)	-18.04	-26.78	-19.70	-12.88	-11.27	-5.69
Net (debt)/cash	16.37	17.28	9.15	0.29	-13.82	-22.46
Equity issues	0.05	13.40	5.53	5.57	0.00	0.00

Source: Hardman & Co Life Sciences Research

Successful Phase I trial with DITEST

Primary and secondary endpoints were met in the Phase I trial

DNL announced that it has met both the primary and secondary endpoints in the Phase I proof-of-concept trial with its oral native testosterone product DITEST in men with primary and secondary hypogonadism. The study (NCT02966652) enrolled 24 adult men, aged between 18 and 80 years old and provides the first evidence of superiority compared with oral testosterone undecanoate, modified-testosterone treatment for patients with hypogonadism.

Results

Results indicated that DITEST would be superior to testosterone undecanoate

The study was designed to evaluate the pharmacokinetic (PK, i.e. level of testosterone) characteristics of DITEST, and to assess the safety and tolerability of the product in the target population. Results indicated that both primary and secondary endpoints were successfully met and suggest that DITEST would be superior to testosterone undecanoate.

Key findings

The study compared a single dose of DITEST (120mg) to oral testosterone undecanoate (80mg) in the fed state in male subjects diagnosed with primary and secondary hypogonadism.

- DITEST showed a more physiological control of levels of testosterone.
- DITEST achieved testosterone levels within the range of healthy men.
- Importantly, DITEST shows similar testosterone absorption in both food and fasted states, according to the FDA guidelines, which is a key differentiator, providing a better testosterone level control.
- Safety and tolerability were established with two doses of DITEST (120mg and 200 mg) with no serious adverse events.
- Higher levels of the potent metabolite dihydrotestosterone (DHT) were seen in the testosterone undecanoate arm.

Oral native testosterone

Specific oral formulation allows it to be administered without the need for a high-fat diet

DNL's specific formulation of native testosterone is designed to be administered orally, being composed of a soft gel, oil-filled, testosterone capsule. This new oily formulation should escape liver metabolism and be easily absorbed by the lymphatic system, increasing its bioavailability. Of particular importance, it demonstrated that this formulation can be administered without the need for a high-fat diet, unlike current oral testosterone undecanoate products.

The Phase I trial

The study consisted of two separate arms of 12 patients each to assess DITEST with the aim: 1) to compare DITEST with the testosterone undecanoate; and 2) to evaluate the bioavailability of DITEST in the fed or fasted states:

- **Cohort 1:** single dose of 120mg DITEST followed by a single dose of 80mg testosterone undecanoate or a single dose of 80mg testosterone undecanoate followed by single dose of 120mg DITEST. The two treatments are separated by a minimum of a seven-day washout period, with both treatments given in the fed state.
- **Cohort 2:** single dose of 200mg DITEST (fed) followed by a single dose of 200mg DITEST (fasted) or a single dose of 200mg DITEST (fasted) followed by single dose of 200mg DITEST (fed). The two treatments are separated by a minimum of a seven-day washout period.

DITEST targets hypogonadal men

DITEST for hypogonadism

Hypogonadism corresponds to a reduction of the function of the gonads (testes and ovaries) that may result in a reduced secretion or the inability to secret sex hormones, the condition affecting men and women. Diurnal, with its oral native testosterone, is only addressing the male hypogonadism market.

Causes

Causes creating hypogonadism are multiples and could be coming from the gland itself (primary hypogonadism) or from an upstream event controlling the gonads (secondary hypogonadism).

Primary hypogonadism

In primary hypogonadism, the testes (or ovaries) themselves do not function correctly. The causes are multiple, as shown in the following table:

Causes of primary hypogonadism	
Certain autoimmune disorders	Radiotherapy / chemotherapy
Genetic and developmental disorders (Klinefelter syndrome)	Surgery
Infection	Injury to the testicles
Liver and kidney disease	

Source: Hardman & Co Life Sciences Research

Secondary hypogonadism

This condition is not due to a dysfunction of the gonads but to an upstream dysfunction that control the gonads. The impairment could be due to the pituitary gland itself or the hypothalamus gland, that controls the pituitary gland. Some of the causes include:

Causes of secondary hypogonadism	
Some medications, including steroids and opiates	Rapid, significant weight loss
Abnormal bleeding	Surgery
Genetic problems	Tumours
Nutritional deficiencies or iron excess (haemochromatosis)	Obesity
Hypopituitarism	

Source: Hardman & Co Life Sciences Research

Symptoms

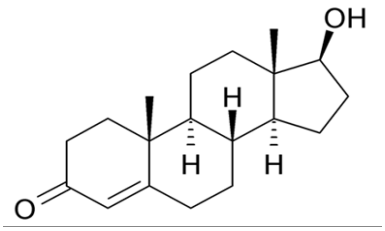
Hypogonadism can begin at any stage of life: from the foetal development, before puberty and during adulthood. During each stage, inadequate hormone stimulation will prevent normal sexual development from occurring. However, hypogonadism manifests differently in males and females and symptoms will differ according to age.

- Abnormal breast development
- Reduced growth of penis and testicles
- Reduced/no sex drive
- Erectile dysfunction
- Hot flushes
- Muscle weakness

Current treatment

Many forms of hypogonadism are treatable and generally have a positive outlook. With the correct treatment, many patients will begin puberty and fertility may be restored. However, treatment plans depend on the gender of the patient and the specific cause of hypogonadism.

Testosterone



Source: Hardman & Co Life Sciences Research

In the US, current treatment of male hypogonadism uses mostly testosterone replacement therapy (TRT), consisting of the delivery of testosterone using topical gel, transdermal patch or by injection. Based on volume, the testosterone replacement market is about 70% topical formulations and about 30% injectable formulations.

Oral products

Interestingly, oral testosterone undecanoate is available in more than 80 countries, with the exception of the US. There are numerous physiological and formulation challenges that have made the development of a commercially viable oral TRT difficult. Oral testosterone is metabolised rapidly and extensively by the intestine and the liver. Consequently, when pharmacological doses of testosterone are taken by mouth, an inadequate amount reaches the bloodstream.

The TRT market is dominated by topical and injectable formulations...

...which have various disadvantages

After being declined in 2015 and an additional Phase III trial requested, the FDA approved Jatenzo from Clarus Therapeutics in March 2019 to treat men with particular forms of hypogonadism. Approval was not easy, as some FDA committee members were worried about the possible off-label use of Jatenzo, and possible cardiovascular risks. The undecanoate formulation makes testosterone more lipophilic, allowing absorption through the intestinal lymphatic system and thereby by-passing liver metabolism. In the US, methyltestosterone (Android, Testred) is the only other approved oral TRT, but is prescribed only occasionally due to high risk of hepatotoxicity.

Other products

Topical products can irritate the patient's skin and can be inconvenient as the patient needs to apply the product to clean, dry skin, thoroughly wash their hands following administration, and wait for the product to dry before they can dress. On the other hand, injectable products can result in wide-ranging blood testosterone levels and associated mood swings, can be painful.

One of the main products on the market is AndroGel (a 1% testosterone gel) from AbbVie, that has had cumulative sales of $7.1bn since its 2010 launch. However, sales have been reducing sharply due to a number of lawsuits, arising from the failure of AbbVie to warn customers about the cardiovascular risks of TRT.

Main testosterone replacement modalities

Product type	Delivery	Regimen	Advantages	Disadvantages
Testosterone undecylate	Oral	40-80mg, 2-3 times daily with meal	Convenient	Variable testosterone concentrations and clinical response; nausea, high DHT/T ratio
Buccal testosterone	Buccal	30mg controlled release	Convenient	Taste disturbance, gum irritation and potential transfer to partner to others
Testosterone esters	Intramuscular	Regimen is dependent of the ester	Low cost, self-administration, corrects hypogonadal symptoms	Highly variable pharmacokinetics, fluctuation in libido and mood, pain at injection sites
Testosterone patch	Transdermal	4-8mg applied nightly to skin	Convenient, mimic circadian rhythm	Sweating interference with patch adherence, skin irritation in 66% of men
Testosterone gel	Transdermal	5-10mg daily	Convenient, mimic circadian rhythm, good skin tolerability	Potential transfer to partner or children, skin irritation, need to cover application site

Source: adapted from Carson Schlich et al 2016, Hosp. Pharm. 51(9), 712-720

The same thing occurred with Depo-testosterone (Pfizer), approved in 1979. The increased marketing and miss-use of these products by customers for muscle growth, athletic performance and to be the "fountain of youth" for men – all medically unapproved uses – has coincided with a rise of strokes and heart attacks. Since September 2015, the FDA ordered drug companies to add warning labels to testosterone products.

The problem with current oral testosterone therapy

While oral testosterone replacement therapies have been available for some time, there is a strong unmet patient need as oral TRT is highly dependent on a high-fat meal for sufficient absorption and adverse toxicity events occasionally occur, including:

- high liver metabolism of testosterone;
- liver toxicity;
- need of high-fat diet to bypass liver metabolism; and
- variability of absorption of testosterone following diet.

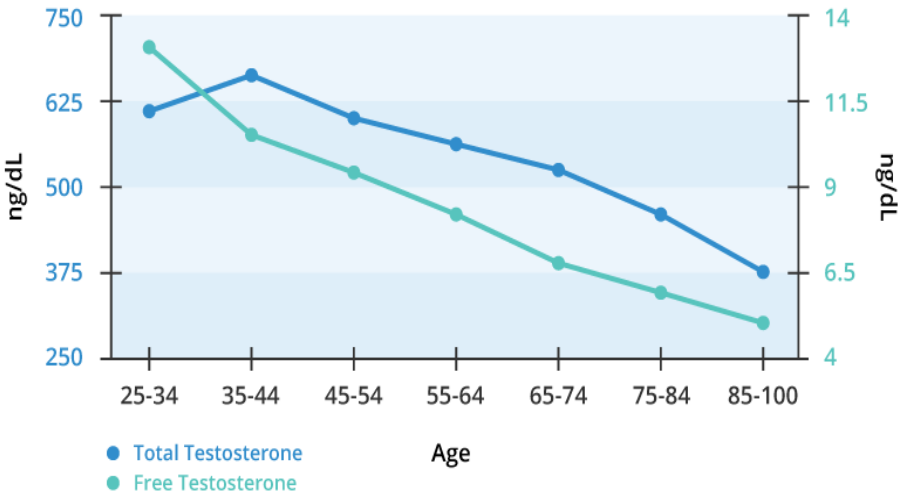
Market opportunity

The global TRT market is estimated to be worth $4.8bn

There is a market opportunity for an oral TRT product that provides a more convenient route of testosterone administration in a formulation that avoids hepatic toxicity. The market is highly fragmented with a number of products utilising alternative routes of administration to the oral route already available. With DITEST, DNL expects to gain a small share of the $4.8bn global market.

The estimates for prevalence vary dramatically between studies based on study designs and inclusion criteria. Clear-cut hypogonadism in young men occurs in approximately 1%. of the population; however, as testosterone levels decline with aging and in the obese, some studies suggest a prevalence of 12% for under 60-year olds, 20% for those in their 60s, 30% in their 70s and 50% in their 80s. With the rates of the aging population rising, and also its association with multiple co-morbid conditions such as, obesity, metabolic syndrome, type 2 diabetes and cardiovascular, it is expected that the prevalence of hypogonadism will increase substantially.

Levels of testosterone in aging men



Source: drugwatch.com

Male hypogonadism is a frequent and potentially undertreated condition. In the US, the condition affects up to four million American men, yet only 5% of potential patients receive treatment. North America and Europe are the largest consumption territories, with market shares of nearly 43% and 12%, respectively, in 2016. According to MarketWatch, the Global Testosterone Replacement Therapy market is valued at $4.8bn in 2018. This adverse growth of the market is the result of various bans on the use of testosterones by various governments across the globe, due to the off-label use, possible side effects, and also the potential role of TRT in prostate cancer.

Conclusion

With DITEST, DNL is progressing a value-added oral testosterone product in primary and secondary hypogonadal men

With the positive Phase I results with DITEST of safety, tolerability and favourable pharmacokinetics in both the fed and fasted states, DNL is progressing a value-added testosterone product in an unmet medical condition of primary and secondary hypogonadal men. The product also showed early signs of superiority over the current oral testosterone undecanoate in a $4.8bn market. DNL revealed that it will soon engage with the US and European regulators for the next phase of clinical trials, which would probably be to be run with a partner.

The next step will be run with a partner

This is the third product that DNL has progressed into the clinic and it is in the process of building on its vision of becoming one of the leading endocrinology speciality pharma companies.

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(Disclaimer Version 8 – Effective from August 2018)

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